DISCRIMINATING FACTORS IN TREATMENT DECISIONS FOR CHEMOTHERAPY IN ELDERLY PATIENTS WITH COLORECTAL CANCER

Mahmood Alam[1], Gabriel Gabriel[2], Michael Barton[3] and Richard Eek[4]

1. Royal Prince Alfred Hospital, Sydney, Australia.

2. Collaboration for Cancer Outcomes Research and Evaluation, Sydney, Australia.

3. South West Sydney Clinical School, University of New South Wales and Collaboration for Cancer Outcomes Research and Evaluation, Sydney, Australia.

4. Cancer Therapy Centre, Liverpool Hospital, Sydney, Australia.

Email: dr_mahmoodalam@hotmail.com

Abstract

Chemotherapy is underutilised in patients over the age of 70 and good arguments exist to support active treatment in this group. We examined patient and disease factors in colorectal cancer patients aged <70 years and 75 years or older that might influence treatment choices independently of age. The data were obtained from LANTIS, the electronic medical record system used at Liverpool and Campbelltown Hospitals. Variables collected included patient demographics and treatment-related factors. It was hypothesised that the difference in utilisation between older and younger patients could be ascribed to confounding factors being more common in the older population. There were 445 patients with colorectal cancer in the years 2005 and 2006. Of these, 267 (60%) were under 70 years of age, 278 (63%) were males and 308 (69%) were married. Two-hundred and ninety-four patients (66%) had colon cancer, 137 (31%) had rectal cancer and 14 (3%) had rectosigmoid cancer. Three-hundred patients received chemotherapy, whereas out of the 137 (31%) who did not, 83 (61%) were in the older age group (75 years or older). Data were missing for eight patients. There was a trend for elderly patients to receive less chemotherapy as compared to the younger cohort. Multivariate regression analyses showed no statistically significant differences for gender, ECOG performance status, socioeconomic status or site of disease. Age was the strongest discriminating factor in chemotherapy decisions of older patients with colorectal cancer.

Advanced age should no longer be considered a reason for not treating older cancer patients.[1] There is both anecdotal and clinical evidence to suggest that treating physicians are reluctant to offer chemotherapy to eligible elderly patients as compared to younger patients.[2] Older patients are also under-represented in clinical trials.[3] Evidence has started to emerge that older people tolerate cancer therapies (both molecular and cytotoxic) as well as younger patients.[4] Are we thus discriminating among our patients, based on their age alone, or are there other factors, such as the presence of comorbities, that lead to a lower uptake of chemotherapy in this group?

In Liverpool and Campbelltown Hospitals, under-utilisation of chemotherapy for patients with colorectal cancer has been documented,[5] and age has been identified as an important predictive factor.[6] The current study was undertaken to explore patient and disease-related factors to determine the differences between younger and older patients. We hypothesised that the difference in utilisation of chemotherapy could be ascribed to confounding factors being more common in the elderly.

Patients and therapy

This was a retrospective study conducted at the Liverpool and Campbelltown Hospitals, Sydney. The data was retrieved from LANTIS, the electronic database used at both hospitals, for the period between January 2005 and December 2006. All new referrals with a diagnosis of colorectal cancer, seen at the two oncology departments were considered for the study, excluding those patients who were already on treatment on or before 1st January 2005.

Approval from Sydney South West Area Health Service Human Research Ethics Committee was obtained. De-identified patient data was grouped into two cohorts, on age criteria (below 70 years of age and 70 years or older). The information collected included patient demographics: age; gender; language spoken; marital status; co-morbidities; ECOG performance status; and disease related factors such as site of disease, TNM stage, treatment received and outcomes. The treatment-related factors were individually extracted from patient medical files recorded electronically at time of consultation and from correspondence. The socioeconomic index was inferred from the postal code of patient residence in line with the guidelines of the Australian Bureau of Statistics. Patients were then grouped into four categories, indicating the increasing degree of social disadvantage using the Index of Relative Socioeconomic Disadvantage (IRSD).

Co-morbidities were recorded as nil, mild, moderate or severe. Mild co-morbidity meant age related co-morbidities only, which were unlikely to affect survival over the next five years. Severe co-morbidity included organ failure or a condition which may reduce five year

survival. ECOG performance status was available for most patients and was inferred for others. ECOG was recorded as unavailable only where no reference was available from the clinical notes or documents.

The decision to treat or not was at the discretion of the treating oncologist. Treatment received was defined as at least one cycle of proposed chemotherapy. In nearly all patients, treatment was accepted by the patient if it was offered. Type of treatment, whether neo-adjuvant, adjuvant or palliative, was also documented and the outcomes were recorded as treatment completed or not.

SPSS (version 15) was used for analyses, Chi square (X^2) tests to examine the relationships between the two cohorts. Univariate and multivariate regression analyses were also performed.

Clinical outcomes

Data from 445 patients with colorectal cancer were collected for the study. Of these, 267 (60%) were under 70 years of age, 278 (63%) were males and 308 (69%) were married (Table 1). ECOG performance status was available for 370 (83%) patients – 78% of patients had good performance status (ECOG 0 or 1). Two hundred and ninety-four (66%) had colon cancer, 137 (31%) had rectal cancer and 14 (3%) had rectosigmoid cancer. At time of first consultation, TNM staging was recorded for 430 (93%) with Stage I (10), Stage II (117), Stage III (172) and Stage IV (131). Data on co-morbidity was available for 442 patients; 142 (32%) had no co-morbidities, 112 (25%) had mild, 132 (30%) had moderate and 56 (13%) had severe co-morbidities.

A total of 300 (67%) patients received at least one cycle of chemotherapy, whereas 137 (31%) did not. Data were not available for eight patients. Two-hundred and eight patients (70%) of those treated were younger than 70 years of age and 83 (61%) of those not treated were 70 years or older (p=0.07).

Patients 70 years or older received significantly less chemotherapy for any stage of disease, any degree of co-morbidity or performance status. It was interesting to note that for a drop in ECOG performance status from 0 to 1, or a mild co-morbidity compared to none, was significantly associated with a much greater decrease in delivered chemotherapy in 70 years or older age group (Table 2).

Forty-five patients received neo-adjuvant treatment, 181 received adjuvant and 142 received palliative treatment. Some patients were given more than one type of chemotherapy. There was no significant difference between patients' age groups for neo-adjuvant, adjuvant or palliative treatment (Figure 1). There was a clear trend for more adjuvant treatments being given to the younger group and more palliative treatments given to the older (Figure 1).

Figure 1: *Types of chemotherapy given to patients by age groups*
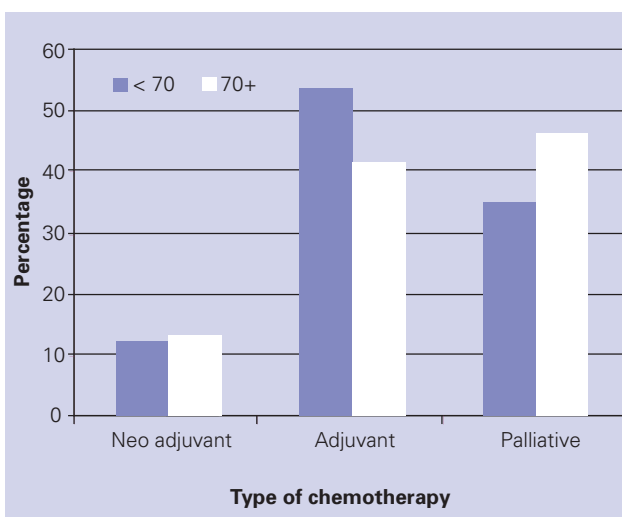
Table I: Patient and disease characteristics

Characteristics		<70 years (n=267)		70+ years (n=178)	
		%	(n)	%	(n)
Status	Alive on 31/12/2006	87	(232)	71	(127)
Gender	Male	64	(170)	61	(108)
	Female	36	(97)	39	(70)
Marital status	Currently married	73	(194)	64	(114)
	Currently not married	27	(73)	36	(64)
Site	Colon	66	(177)	66	(117)
	Rectum	31	(82)	31	(55)
	Rectosigmoid	3	(8)	2	(6)
Stage	Stage I	2	(5)	3	(5)
	Stage II	27	(71)	26	(46)
	Stage III	42	(112)	34	(60)
	Stage IV	27	(73)	33	(58)
	Unknown	2	(6)	5	(9)

FORUM

		<70 %	70+ %	P value
Gender	Male	79	54	0.50
	Female	75	49	
Currently Married	Yes	79	59	0.01
	No	75	39	
IRSD	1	75	51	<0.001
	2	80	58	0.02
	3	85	44	<0.0001
	4	77	56	0.3
ECOG	0	82	87	0.5
	1	81	59	0.02
	2	78	26	0.02
	3	56	28	0.3
Co-morbidity	Mild	80	68	0.1
	Moderate	85	56	<0.001
	Severe	57	27	0.02
	Any	78	52	<0.0001
Stage	I	60	40	1
	II	54	37	0.8
	III	93	65	<0.0001
	IV	85	59	<0.001
	U	17	0	–

A subgroup analysis was conducted on only stage III and IV patients because the indications for chemotherapy are more clear-cut, however the results were very similar to earlier analysis on the two groups which included all stages (Tables 3 and 4).

In the multivariate regression analysis, a significant association between the likelihood of receiving chemotherapy was observed for Stage III and IV (3.4 times, p<0.001), no co-morbidity (1.7 times, p=0.028), currently married (1.7 times p<0.007) and for age <70 years (3.3 times, p<0.0001). Gender, Index of Relative Socioeconomic Disadvantage (IRSD/SES) and anatomical site of disease did not show significant difference.

Implications

Bowel cancer is second only to lung cancer as the most common cause of cancer related deaths in males and females combined. It is estimated that one in 17 males and one in 26 females will develop bowel cancer by age 75.[7] Age is unmodifiable and is perhaps the most important risk factor associated with bowel cancer.[8] In New South Wales the median age at diagnosis for bowel cancer in 2004 was 69 years for males and 72 years for females. The 70 years or older age group is a large proportion of bowel cancer patients. The current study is unique, as it looks particularly at this cohort and explores the utilisation of chemotherapy (for all stages) in relation to patient age and co-morbidities. The authors were unable to apply more stringent criteria to document co-morbidities, due to the retrospective nature of the study and limitation of how these were indexed at the time of initial consultation.

Australian guidelines recommend offering chemo-therapy to Stage III and IV patients, but controversy exists about treating Stage II. A consensus is now emerging among the treating oncologists on identifying a higher risk group who would benefit from treatment. The proportion of Stage II cases in the current study was similar in the two age groups.

The low proportion of older (70 years or older) patients receiving chemotherapy was not due to older patients being more likely to refuse chemotherapy if it was offered. In fact very few patients refused chemotherapy if it was offered to them. Our study showed that even after accounting for differences in performance status and co-morbidities, patients over 70 years of age were less likely to be offered chemotherapy. A similar pattern was reported in US.[9]

There could be a selection bias with those patients who are unlikely to undergo surgery being referred for chemotherapy. To examine this we compared the proportions for each stage in our study with data from the Sydney South-west Area Health Service Cancer Registry. The percentage of cases identified were Stage I, 15%; II, 33%, III, 32% and IV 19% respectively. Apart from a lower number of Stage I patients in our study, a high proportion of Stage II and nearly all Stage III and IV were referred for a chemotherapy opinion.

The study was not designed to show a survival advantage of those receiving chemotherapy, as follow-up was not long enough.

Table 3: *Proportion of patients with stage III and stage IV disease, who received chemotherapy (by age groups)*

Patient Characteristics		Received Chemo		Age groups		Total	P
				Below 70 yrs	70+ yrs		
Sex	Male	Yes	Count	104	44	148	
			%	70	29	100	
	Female		Count	62	29	91	
			%	68	32	100	
	Total		Count	166	73	239	
			%	69	31	100	
	Male	No	Count	9	27	36	p<0.0001
			%	25	75	100	
	Female		Count	10	18	28	P=0.03
			%	36	64	100	
	Total		Count	19	45	64	p<0.0001
			%	30	70	100	
Marital status	Currently married	Yes	Count	126	53	179	
			%	70	30	100	
	Currently not married		Count	40	20	60	
			%	67	33	100	
	Currently married	No	Count	8	21	29	p<0.001
			%	28	72	100	
	Currently not married		Count	11	24	35	P=0.002
			%	31	69	100	
Co-morbidity	No	Yes	Count	63	14	77	
			%	82	18	100	
	Yes		Count	103	59	162	
			%	64	36	100	
	No	No	Count	8	18	26	P=0.006
			%	31	69	100	
	Yes		Count	11	27	38	p<0.001
			%	29	71	100	

Conclusions

Younger patients (<70yrs) with Stage III or IV disease, no co-morbidities and married patients were more likely to receive chemotherapy than older patients. We could not show that confounding factors significantly predicted the treatment making decisions for older patients and age was the strongest discriminating factor. It also seems that the 70 years or older age group may be missing out on more curative treatments as compared to patients <70 years. We strongly recommend that a more stringent approach be taken in this particular group and a proper geriatric assessment be done to determine the physical status of those patients who may benefit from potentially curable treatments before ruling them out on basis of age alone. We also recommend more participation of this age group in randomised control trials to determine the impact on survival benefit in those undertaking chemotherapy.

FORUM

Patient performance status		Received chemo		Age groups		Total	P
				Below 70 yrs	70+ yrs		
ECOG	0	Yes	Count	95	20	115	
			%	83	17	100	
	1		Count	33	28	61	
			%	54	46	100	
	2		Count	6	7	13	
			%	46	54	100	
	3		Count	3	6	9	
			%	33	67	100	
	Total		Count	137	61	198	
			%	69	31	100	
	0	No	Count	5	1	6	P=0.08
			%	83	17	100	
	1		Count	3	8	11	P=0.03
			%	27	73	100	
	2		Count	2	11	13	P<0.001
			%	15	85	100	
	3		Count	3	14	17	P<0.001
			%	18	82	100	
	4		Count	1	3	4	P=0.5
			%	25	75	100	
	Total		Count	14	37	51	P<0.0001
			%	27	73	100	

References

1   Bernardi D. Insight into the treatment of cancer in older patients: developments in the last decade. Cancer Treatment reviews 32 (4) :277-88, 2006 Jun.

2   Mahoney T. et al. Stage III Colon cancers: Why adjuvant chemotherapy is not offered to elderly patients. Archives of Surgery. 135(2): 182-5, 2000 Feb

3   Townsley CA. et al. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. J Clin Onc, 23(13): 3112-24, 2005 May1.

4   Townsley CA. et al. Evaluation of adverse events experienced by older patients participating in studies of molecularly targeted agents alone or in combination. Clinical Cancer Research. Vol 12: 2141-9, 2006 Apr.

5   Asghari, G. et al. Estimation of an optimal chemotherapy utilization rate in colorectal cancer (CRC) 2006 Gastrointestinal Cancers Symposium, American Society of Clinical Oncology.

6   Ng W, Gabriel G, Moylan E. Predictive Factors for the Underutilization of Adjuvant Chemotherapy in Colon Cancer in South western Sydney. CTC Liverpool Hospital, CCORE, Sydney, Australia.

7   Duncombe J. Bowel Cancer in New South Wales. Dec 2007, Cancer Institute Report.

8   Gross, CP; 2006. Multimorbidity and survival in older persons with colorectal cancer. Journal of American geriatric Society, 54 (12): 1898-1904.

9   National Cancer Database. Commission on Cancer, ACoS. Benchmark Reports, v1.1 – October 1, 2007.